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GLP-1 receptor agonists in diabetes and weight loss: the double-edged sword of innovation and risks

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In recent years, glucagon-like peptide-1 (GLP-1) receptor agonists have gained widespread popularity not only as effective agents in the management of type 2 diabetes but also for their beneficial impact on weight loss. Additionally, this surge in interest has been underpinned by their pleiotropic effects and has spurred further investigation into their potential applications beyond diabetes care. However, the expanding adoption of GLP-1 receptor agonists also brings with it a set of challenges and complications. With promising therapeutic effects comes an increased scrutiny on side effects.

GLP-1 receptor agonists mimic the action of the native GLP-1 peptide, enhancing insulin secretion, suppressing glucagon release, slowing gastric emptying, and increasing satiety. Initially introduced to treat diabetes, they were also found to have an important effect on weight loss; a paradigm shift in the medical management of obesity may - in fact - be imminent, per the opinion of medical and non-medical pundits (1–3). Drugs like semaglutide, liraglutide or tirzepatide (a dual GLP-1 and GIP analog) have led to significant weight reduction of participants in clinical trials and in real-world settings, making them popular for patients and physicians alike.

The success of GLP-1 receptor agonists in weight management lies in their multifaceted mechanisms, which address complex physiological pathways of hunger, satiety, and glucose metabolism. These drugs target not only the pancreas and gut but also the brain's hypothalamic appetite-regulating centers. Some of the effects of GLP-1 analogs may be attributed to their actions on central nervous system neurotransmitter secretion/action; they enhance gamma-aminobutyric acid (GABA) activity, restore dopaminergic activity and act in parallel with peptide YY (PYY) (4–6). In this sense, GLP-1 analogs are redefining the therapeutic approach to metabolic disease by not only addressing glycemic control but also influencing body weight and cardiovascular health. Currently, long-term consequences of GLP-1 analog use for over 1.5–2 years look promising; in published meta-analyses,

reduced cardiovascular morbidity and mortality have been noted, whereas no effect on the appearance of gastrointestinal neoplasia has been observed (7, 8).

The pleiotropic effects of GLP-1 analogs foster ongoing research into new indications. Evidence suggests these drugs may also have potential cardiovascular benefits, with studies indicating reduced cardiovascular risk among people with type 2 diabetes who use GLP-1 receptor agonists (9–12). Additionally, studies have explored the impact of GLP-1 receptor agonists on liver health, including potential benefit in the treatment of metabolic dysfunction associated fatty liver disease (MASLD) (13, 14). The anti-inflammatory and neuroprotective properties of GLP-1 analogs are also being investigated, with implications for neurodegenerative conditions like Alzheimer's disease (15–17). Such research raises the possibility of broader therapeutic applications for GLP-1 receptor agonists, as their influence extends beyond traditional diabetes and weight management.

As exciting as these advancements are, they raise critical questions about society's preference for pharmacological solutions over traditional lifestyle interventions like diet and exercise. In the mindset of many patients and practitioners, the allure of weight-loss medications may indeed outweigh the need for lifestyle changes, despite evidence that diet and physical activity are fundamental components of sustainable health. Surveys of internet use worldwide have indicated a frank increase in searches for these new drugs (18, 19). However, it has also been revealed that people are more interested in pharmaceutical solutions for weight loss than in making significant lifestyle modifications. This trend is fueled by the relative ease and accessibility of medications, coupled with the perception that they can yield rapid, visible results (traditional and social media and statements by “celebrities” may add to this trend).

Pharmaceutical companies have responded to this demand with a pipeline of weight-loss drugs, many of which are based on the mechanisms of GLP-1 receptor agonists. This focus on pharmacotherapy, however, risks overshadowing the essential role of non-pharmacological interventions in chronic disease prevention and management. It is important for healthcare providers to emphasize that while medications like GLP-1 analogs can play a valuable role in treatment plans, they are not substitutes for a balanced diet, regular physical activity, and other lifestyle modifications.

While GLP-1 analogs are largely considered safe, their increasing usage has drawn attention to rare but significant adverse events. Nonarteritic anterior ischemic optic neuropathy (NAION), an idiopathic ischemic injury to the optic nerve head, marked by sudden, painless vision loss in the eye and swelling of the optic disc, has been reported in association with GLP-1 receptor agonists' use, though such cases remain rare (20). The mechanisms by which GLP-1 analogs might trigger NAION are not yet fully understood, and further investigation is necessary to determine whether a causal relationship exists. In clinical practice, patients experiencing visual disturbances while on GLP-1 analog therapy should be evaluated promptly, with consideration given to discontinuing the medication if a link is suspected.

Pancreatitis is a known potential risk associated with GLP-1 receptor agonists. Although the absolute risk is low, pancreatitis can be severe and even life-threatening. GLP-1 receptors are expressed

in the pancreas, which has led researchers to hypothesize that these drugs may influence pancreatic function in ways that could predispose certain individuals to inflammation. Studies on this association have yielded mixed to negative results (21–23), and while there is no definitive evidence linking GLP-1 receptor agonists to a higher incidence of pancreatitis, it remains a listed adverse effect.

Other significant adverse events, possibly linked to the use of GLP-1 analogs, include muscle mass loss, dermatological/hypersensitivity reactions, increased heart rate, reduced left ventricular ejection fraction and depression (24–26).

The emergence of these safety concerns reinforces the importance of individualized patient assessment before prescribing GLP-1 receptor agonists, particularly for those with a history of pancreatic disorders or other risk factors. Healthcare providers must engage in thorough discussions with patients, weighing the potential benefits against the risks and ensuring that patients understand the signs and symptoms of adverse events. The advent of GLP-1 receptor agonists represents a milestone in the treatment of diabetes and obesity, but it also presents a challenge in balancing the drive for innovation with the need for patient safety. These medications, like many in the pharmaceutical landscape, are not devoid of risks, and their popularity should not detract from the importance of comprehensive, individualized care. While GLP-1 analogs offer much promise, they also underscore the reality that pharmacotherapy alone cannot address the root causes of chronic metabolic diseases. As we move forward, it will be crucial to develop a nuanced approach to the prescription of GLP-1 receptor agonists and other weight-loss drugs. Educating patients about the importance of lifestyle modification, as well as the potential risks of pharmacotherapy, will remain essential. Additionally, further research is needed to clarify the mechanisms underlying adverse events and to identify which patients may be at higher risk (27).

GLP-1 receptor agonists have transformed the landscape of diabetes and obesity management, offering significant benefits that extend beyond glycemic control. However, the increasing reliance on pharmacological solutions over lifestyle interventions reflects a broader societal trend that risks de-emphasizing the role of diet and exercise in managing chronic diseases. The potential for adverse effects like NAION and pancreatitis, although rare, serves as a reminder of the complexities of drug therapy and the need for careful patient selection and monitoring. In our pursuit of medical advancements, the allure of innovative pharmacotherapies like GLP-1 analogs should be balanced with a commitment to safe and responsible practice. As healthcare providers, our responsibility is not only to embrace the tools that modern medicine provides but also to remain vigilant in safeguarding patient health through informed, evidence-based care. The promise of GLP-1 analogs is undeniable, yet so is the need for caution and judicious use in our quest to improve patient outcomes.

Author contributions

II: Conceptualization, Investigation, Project administration, Resources, Supervision, Validation, Writing – original draft,

Writing – review & editing. LZ: Investigation, Methodology, Writing – original draft, Writing – review & editing. MR: Conceptualization, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Writing – original draft, Writing – review & editing.

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